

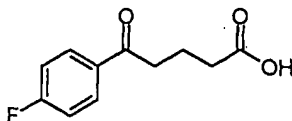
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**PROCESS FOR THE PREPARATION OF
4-(4-FLUOROBENZOYL) BUTYRIC ACID**

5 INTRODUCTION

The present invention relates to an improved process for the preparation of 4-(4-fluorobenzoyl)butyric acid. The 4-(4-fluorobenzoyl)butyric acid has the formula-I given below.



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The 4-(4-fluorobenzoyl)butyric acid has the formula-I is a key raw material for the synthesis of anti-hyperlipoproteinemic drug ezetimibe (US 5767115, Schering). The main criticality in making the compound of formula-I lies in controlling the desfluoro analogue impurity (4-benzoylbutyric acid) at an acceptable level (< 0.05% w/w by HPLC).

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BACKGROUND OF THE INVENTION

20 In the literature only two procedures are known for the preparation of compound of formula-I. In the first procedure reported by Compernelle (Tetrahedron, 49, 3193, 1993) fluorobenzene is reacted with glutaric anhydride under Friedel-Crafts conditions using aluminium chloride at 0°C to get the compound of formula-I in 78% yield. The reaction is done in methylene chloride medium. In this procedure reaction was done on a 15gr
25 glutaric anhydride scale. The quality of final product with respect to impurities is not addressed in this reference. The main drawbacks in this procedure are:

1. Temperature of the reaction (0°C) is not suitable for scale up operations. At 0°C aluminum chloride-glutaric anhydride complex is not soluble in the medium and a thick mass (difficult to stir by mechanical stirrer) will form. Because of improper mixing quality and yield of the product is low.
 2. Quenching of Friedel-Crafts reaction by adding water or acid to the reaction mass is difficult on a larger scale.
 3. Quality of fluorobenzene used in the process is not mentioned. This is very critical to get an acceptable quality of compound of formula-I with respect to desfluoro analogue impurity.
- In the second route (US patent, 6,207,822) for the synthesis of compound of formula-I, fluorobenzene is used as a solvent-cum-reagent in the Friedel-Crafts acylation with glutaric anhydride. The yield of compound of the formula-I reported in this procedure is 79%. The reaction is done at 5-12°C. The main disadvantages in this process are:
1. It requires high quality (benzene content in fluorobenzene should be less than 100ppm) fluorobenzene to get acceptable quality compound of formula-I.
 2. Availability of high quality fluorobenzene is limited for employing the process on a commercial scale.
 3. Price of high quality fluorobenzene is almost 4 times higher than the normal quality (benzene content is 300-700ppm) fluorobenzene. Normal quality fluorobenzene is abundantly available in the market.

Keeping in view of the above mentioned difficulties in implementing the above routes for making compound of formula-I on a commercial scale, we directed our research work to develop a simple, convenient, and economical process for the preparation of compound of formula-I which can also be utilized on a commercial scale

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The main objective of the present invention is, therefore, to provide an improved process for the preparation of compound of formula-I as defined above overcoming all the disadvantages present in the hitherto known processes.

- 10 Another objective of the present invention is to provide an improved process for the preparation of compound of formula-I as defined above which is simple and economical.

Another objective of the present invention is to provide an improved process for the preparation of compound of formula-I as defined above which does not have any mixing

- 15 problem when the process is used on any scale of operation.

Another objective of the present invention is to provide an improved process for the preparation of compound of formula-I as defined above which does not have reaction quenching problem when the process is used on any scale of operation.

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Still another objective of the present invention is to provide an improved process for the preparation of compound of formula-I as defined above which does not require high quality fluorobenzene.

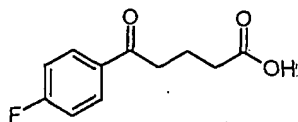
- 25 Another objective of the present invention is to provide an improved process for the preparation of compound of formula-I as defined above which does not require fluorobenzene as solvent medium to carry out the Friedel-Crafts reaction.

SUMARY OF INVENTION

In our preliminary studies in the course of the R&D towards development of an improved process for the preparation of compound of formula-I as defined above we found that benzene is more reactive (about 5 times) than fluorobenzene in the above mentioned Friedel-Crafts acylation. This indicates that benzene present in fluorobenzene will react faster than fluorobenzene. Considering this observation we found that

- (i) by adjusting the ratio of fluorobenzene with regard to the glutaric anhydride used,
 - 10 (ii) dividing the amount of fluorobenzene used into two parts - one along with glutaric anhydride and another part with the halogenated solvent and
 - (iii) fixing the quantity of the halogenated solvent used,
- a process can be developed for the preparation of compound of the formula-I as defined above which overcomes the drawbacks of the hitherto known processes described above,
- 15 Further the process developed can also be useful for any commercial scale production of the said compound of the formula-I. The reaction can be conducted at a convenient temperature range of 10 to 25°C.

Accordingly, the present invention provides an improved process for the preparation of compound (4-(4-fluorobenzoyl)butyric acid) of the formula-I



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which comprises:

- 25 (a) Preparing a solution of normal quality fluorobenzene, glutaric anhydride and halogenated solvent, the amount of fluorobenzene used being in a molar ratio of 0.5 to 0.7 molar equivalent with regard to the amount of glutaric anhydride used.

- (b) Preparing a mixture of aluminum chloride, normal quality fluorobenzene and halogenated solvent, the amount of fluorobenzene used being in a molar ratio of 0.5 to 0.6 molar equivalent with regard to the amount of glutaric anhydride used and the amount of halogenated solvent used being at least 4-6 times (w/v) with regard to the amount of glutaric anhydride used.
- (c) Adding the solution obtained in step (a) to the mixture obtained in step (b) at a temperature in the range of 10 to 25°C.
- (d) Maintaining the resulting reaction mixture at a temperature in the range of 10 to 25°C for a period in the range of 2 to 4hrs.
- (e) Pouring the reaction mixture into cold dilute hydrochloric acid.
- (f) Distilling the halogenated solvent at atmospheric pressure for its recovery.
- (g) Filtering and washing the residue with the same halogenated solvent used in step (b) above to obtain the compound of the formula-I.
- (h) Purifying the compound of the formula-I by dissolving it in aqueous base and precipitating the product by acidification after giving a carbon treatment to the basic solution.
- (i) Isolating the precipitated compound of formula-I by filtration and if desired
- (j) Recrystallizing the purified acid from a single or mixture of solvents.
- The normal quality of fluorobenzene used in step (a) refers to the impurity level of benzene. The benzene content in fluorobenzene may be between 300-700ppm. The halogenated solvent used in step (b) may be selected from methylene chloride, ethylene dichloride, 1,1,2,2-tetrachloroethane. The base used in step (h) may be selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, and ammonia. The acid used in step (h) may be selected from hydrochloric acid, hydrobromic acid, sulfuric acid, acetic acid, and propionic acid. The solvent used for recrystallization in step (j) may be selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, toluene, acetonitrile, methanol, ethanol, ethyl acetate, hexane or a mixture of these solvents.

The details of the invention are described in Examples given below which are provided to illustrate the invention only and therefore should not be construed to limit the scope of the present invention.

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Example 1

Preparation of 4-(4-fluorobenzoyl)butyric acid of formula-I using fluorobenzene (benzene content 300ppm) with methylene chloride as solvent:

10 Into a 3L three-necked RB flask were charged 500ml of methylene chloride, 250gr of aluminum chloride and 45gr of fluorobenzene (benzene content 300ppm) under nitrogen atmosphere. The reaction mixture was cooled to 10°C and a solution of 100gr of glutaric anhydride, 45gr of fluorobenzene (benzene content 300ppm) and 500ml of methylene chloride was added slowly over a period of 3hrs between 10-15°C. The reaction mixture
15 was maintained for another one hour at the same temperature. The reaction mixture was slowly poured onto a mixture of crushed ice (700gr) and conc. HCl (300ml) below 10°C. The reaction mass temperature was allowed to reach 25°C and methylene chloride distilled off from the reaction mixture below 50°C. After cooling the reaction mixture to 20°C, solids were filtered off and washed with 500ml of water.

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The wet cake thus obtained was suspended in 250-300ml of methylene chloride and filtered. The solid compound was dissolved in 600ml of 4% sodium hydroxide, treated with 10gr of activated charcoal and filtered. The filtrate was acidified with conc. HCl and the precipitated acid was filtered. After washing the wet cake with 500ml of water, it was
25 dissolved in 500ml of acetone. The acetone solution was slowly cooled to 15-20°C and the solid filtered, washed with chilled acetone (50ml) and dried at 50-70°C to get 122gr of white crystalline solid, m.p. 143°C. Purity by HPLC is 99.65%. Desfluoro impurity is less than 0.05%.

Example 2

**Preparation of 4-(4-fluorobenzoyl)butyric acid of formula-I using
5 fluorobenzene (benzene content 500ppm) with methylene chloride as
solvent:**

Into a 3L three-necked RB flask were charged 500ml of methylene chloride, 250gr of
aluminum chloride and 45gr of fluorobenzene (benzene content 500ppm) under nitrogen
10 atmosphere. The reaction mixture was cooled to 10°C and a solution of 100gr of glutaric
anhydride, 45gr of fluorobenzene (benzene content 500ppm) and 500ml of methylene
chloride was added slowly over a period of 3hrs between 10-15°C. The reaction mixture
was maintained for another one hour at the same temperature. The reaction mixture was
slowly poured onto a mixture of crushed ice (700gr) and conc. HCl (300ml) below 10°C.
15 The reaction mass temperature was allowed to reach 25°C and methylene chloride
distilled off from the reaction mixture below 50°C. After cooling the reaction mixture to
20°C, solids were filtered off and washed with 500ml of water.

The wet cake thus obtained was suspended in 250-300ml of methylene chloride and
20 filtered. The solid compound was dissolved in 600ml of 4% sodium hydroxide, treated
with 10gr of activated charcoal and filtered. The filtrate pH was adjusted to 1.0-2.0 with
conc. HCl and the precipitated acid of formula-I was filtered. After washing the wet cake
with 500ml of water, it was dissolved in 500ml of acetone. The acetone solution was
slowly cooled to 15-20°C, maintained for 2h, and the solid filtered, washed with chilled
25 acetone (50ml) and dried at 50-70°C to get 120gr of white crystalline solid of formula-I,
m.p. 143-143.5°C. Purity by HPLC is 99.7%. Desfluoro impurity is less than 0.05%.

Example 3

**Preparation of 4-(4-fluorobenzoyl)butyric acid of formula-I using
5 fluorobenzene (benzene content 700ppm) with methylene chloride as
solvent:**

Into a 3L three-necked RB flask were charged 500ml of methylene chloride, 250gr of
aluminum chloride and 45gr of fluorobenzene (benzene content 700ppm) under nitrogen
10 atmosphere. The reaction mixture was cooled to 10°C and a solution of 100gr of glutaric
anhydride, 45gr of fluorobenzene (benzene content 700ppm) and 500ml of methylene
chloride was added slowly over a period of 3hrs between 10-15°C. The reaction mixture
was maintained for another one hour at the same temperature. The reaction mixture was
slowly poured onto a mixture of crushed ice (700gr) and conc. HCl (300ml) below 10°C.
15 The reaction mass temperature was allowed to reach 25°C and methylene chloride
distilled off from the reaction mixture below 50°C. After cooling the reaction mixture to
20°C, solids were filtered off and washed with 500ml of water.

The wet cake thus obtained was suspended in 250-300ml of methylene chloride and
20 filtered. The solid compound was dissolved in 600ml of 4% sodium hydroxide, treated
with 10gr of activated charcoal and filtered. The filtrate pH was adjusted to 1.0-2.0 with
conc. HCl and the precipitated acid of formula-I was filtered. After washing the wet cake
with 500ml of water, it was dissolved in 500ml of acetone. The acetone solution was
slowly cooled to 15-20°C, maintained for 2h, and the solid filtered, washed with chilled
25 acetone (50ml) and dried at 50-70°C to get 123gr of white crystalline solid of formula-I,
m.p. 143°C. Purity by HPLC is 99.6%. Desfluoro impurity is less than 0.05%.

Example 4

**Preparation of 4-(4-fluorobenzoyl)butyric acid of formula-I using
5 fluorobenzene (benzene content 500ppm) with ethylene dichloride as
solvent:**

Into a 3L three-necked RB flask was charged ethylene dichloride (500ml), aluminum
chloride (250gr) and fluorobenzene (45gr) under nitrogen atmosphere. The reaction
mixture was cooled to 10°C and a solution of glutaric anhydride (100gr), fluorobenzene
10 (45gr) and ethylene dichloride (500ml) was added slowly over a period of 3hrs between
10-15°C. After maintaining for one hour at 15-18°C the reaction mixture was slowly
poured onto a mixture of crushed ice (700gr) and conc. HCl (300ml) below 10°C. The
reaction mass temperature was raised to reach 25°C and distilled off ethylene dichloride
from the reaction mixture below 100°C. After cooling the reaction mixture to 20°C, crude
15 solid was filtered off and washed with 500ml of water.

The wet cake thus obtained was suspended in 300ml of ethylene dichloride and filtered.
The solid compound was dissolved in 600ml of 4% sodium hydroxide, treated with 15gr
of activated charcoal and filtered. The filtrate was acidified to pH 1.5-2.0 with conc. HCl
20 and the precipitated acid was filtered. After washing the wet cake with 500ml of water, it
was dried at 60-70°C to get 130gr of white solid, m.p. 140-142°C. This solid was
dissolved in 500ml of acetone. The acetone solution was slowly cooled to 15-20°C and
the solid filtered, washed with chilled acetone (50ml) and dried at 50-70°C to get 120gr
of white crystalline solid, m.p. 143°C. Purity by HPLC is 99.65%. Desfluoro impurity is
25 less than 0.05%.

Advantages of the present invention:

1. (a) By adjusting the ratio of fluorobenzene with regard to the glutaric anhydride used
(b) dividing the amount of fluorobenzene used into two parts - one along with glutaric
5 anhydride and another part with the halogenated solvent and (c) conducting the
Friedel-Crafts acylation at 10-20°C, the process can be made applicable to any scale
of operation.
2. By using halogenated solvent in the reaction, quality of required fluorobenzene could
10 be relaxed to normal quality to make the process economical.
3. High quality compound of formula-I could be produced using normal quality
fluorobenzene.